Editorial Comment

Stroke in Young People—The Heart of the Matter

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Not long ago, it was the conventional wisdom that ischemic strokes in young people were tragic curiosities of unfathomable cause and with a benign prognosis. New concepts of pathogenesis combined with diagnostic advances and careful study of large numbers of such patients have challenged these traditional views. In recent clinical series, a likely cause of brain infarction has been identified in 67% to 91% of young people with stroke.[1-5] In the past decade, several new causes of ischemic stroke have been recognized and other, previously known causes further defined and emphasized. Considerable attention has focused on arterial dissection, the prothrombotic state associated with lupus anticoagulants and especially embolism related to mitral valve prolapse and occult cardiac disorders.

Arterial dissections of the cervical carotid and vertebral arteries are an important cause of stroke in otherwise healthy young adults, accounting for 4% to 22% of brain infarcts.[1-3,6] Once believed to be quite rare, with only a handful of cases reported before 1975, several hundred cases of patients with dissections have been reported in the past decade. Dissection occurs when blood extrudes into the arterial wall, collecting subintimally or intramedially and resulting in compression of the true lumen. Unusual neck torsion or trauma, though often quite minor, precedes the onset of symptoms in many patients, particularly those with vertebral artery dissections.[6] The hallmark of cervical carotid artery dissection is prominent pain in the ipsilateral neck, face or head, coupled with brain ischemia in a relatively young person (mean age about 40 years). An ipsilateral partial Horner's syndrome (oculosympathetic paresis) is present in half of patients. Pathologic studies have failed to identify underlying arterial abnormalities predisposing to dissection in most patients, although fibromuscular dysplasia and related intimal abnormalities have been associated with multiple and recurrent dissections.

Recent interest and enthusiasm have led to erroneous overdiagnosis of cervical carotid artery dissection, based on nonspecific arteriographic abnormalities. The arteriographic features of carotid dissection have been recently reviewed.[6-9] As emphasized by Fisher and co-workers in 1978, a tapered occlusion of the cervical carotid artery is the least specific arteriographic abnormality and does not strongly suggest dissection unless reflux into the ipsilateral carotid siphon can be shown via collateral filling.[7] In our experience, emboli lodging at the internal carotid artery bifurcation are a more common cause of tapered cervical carotid artery occlusion (due to retrograde thrombosis) than are dissections. Any cause of distal carotid occlusion can produce this arteriographic abnormality.[6] Casual diagnosis of any and all unusual, nonspecific arterial lesions as dissection has led to frequent errors in management and considerable obfuscation in the literature.

The role of prothrombotic states as a cause of stroke in young people has long been postulated, but laboratory markers have been elusive.[10] Recent attention has focused on the association of lupus anticoagulants and related antiphospholipid antibodies with otherwise unexplained thrombosis, both venous and arterial.[1,11-13] Lupus anticoagulant is a double misnomer. Although initially characterized in patients with systemic lupus, most patients who harbor these antibodies do not have the disease. While these antibodies cause the activated partial thromboplastin time (APTT) to be prolonged in vitro, they are associated with thrombosis, not bleeding, in vivo. The antibodies responsible for the prolongation of the APTT, the conventional laboratory marker of lupus anticoagulant, appear to be a subset of a larger, heterogeneous group of antiphospholipid antibodies that are also associated with thrombosis. Young adults with otherwise unexplained stroke have been described who do not have lupus anticoagulants (defined by abnormal results of an APTT dilution test) but who do have antiphospholipid antibodies.[13] Further exploration of the association between antiphospholipid antibodies and unexplained stroke is needed to define whether a causal relation exists and, if so, the mechanism, natural history and optimal treatment.

Cardiogenic embolism accounts for about a third of strokes in young people.[1] While the cardioembolic source is often apparent, it may be occult.[1,2,14-16] A diagnosis of cardiogenic brain embolism is difficult to establish with certainty when the embolic source is inapparent, requiring a constellation of clinical features, none of which is individually specific.[17,18] The abrupt onset of the maximal neurologic deficit, sometimes associated with a transient loss of consciousness, is suggestive of cardioembolic stroke. Multiple cortical brain infarcts in different arterial distributions, especially if found to be hemorrhagic on computed tomographic scans, support a cardioembolic stroke mechanism.[17] Serial arteriography, if initially carried out within 24 to 48 hours of stroke onset, can occasionally demonstrate migration of embolic fragments, the most specific clinical feature. The lack of diagnostic features that are highly specific or quantitatively validated is a major, unresolved clinical problem. The diagnosis of cardioembolic stroke has often been missed.[19] New diagnostic techniques to image cardiac thrombi or cardiac disorders predisposing to thrombi (or both) have allowed improved detection of occult embolic sources and more accurate diagnosis.[16,20-23]

Mitral valve prolapse has been associated with ischemic stroke in young adults.[17,24] The presumed mechanism is em-

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bolism of aseptic thrombi that form on the fissured surface of the myxomatous and redundant valve leaflets; a cardioembolic mechanism is supported by the handful of autopsied cases.[25,26] Mitral valve prolapse is a common disorder in healthy young people without stroke, present in about 5% of men and as many as 15% of young women, depending on echocardiographic criteria.[27] While the risk of ischemic stroke is increased in young adults with mitral valve prolapse, the absolute risk remains very low (estimated at 1 stroke per 5,000 young people per year), and no antithrombotic prophylaxis is warranted in asymptomatic young adults with mitral valve prolapse.[28] Similarly, when a young adult with ischemic stroke is found to have mitral valve prolapse, a cause-effect cannot be assumed until other causes of stroke have been vigorously excluded. Even then, the diagnosis should be viewed with skepticism, as mitral valve prolapse is coincidental in about half of young adults with stroke who harbor this common condition. No auscultatory or echocardiographic features have yet been elucidated that distinguish embolism-prone mitral valve prolapse from the more common benign form. Preliminary observations suggest that thickening of the leaflets and concomitant aortic valve prolapse may be predictive.[29] In young adults with an initial stroke attributed to mitral valve prolapse, the risk of recurrent stroke is surprisingly low,[30] although in a few patients recurrent emboli and progressive valvular insufficiency may necessitate valve replacement.[31]

In young stroke victims with no clear cause of stroke following initial diagnostic testing, what further cardiac investigations should be done? Two-dimensional echocardiography sensitively detects large ventricular thrombi, but is less useful for small ventricular thrombi and thrombi in the atrial appendage.[32,33] Small (2 to 4 mm) thrombi in the ventricular apex, especially if they have a flat, plaquelike configuration, are easily missed by echocardiography, but yet can embolize to cause devastating strokes. Wall-motion abnormalities are often apparent when thrombi are too small to be directly visualized. Transesophageal echocardiography appears to allow detection of atrial thrombi not visualized by standard techniques.[33] The relative sensitivity of magnetic resonance imaging[23] and isotope-labeled platelet studies[20] compared with echocardiography is not yet fully defined. Contrast echocardiography will detect atrial septal defects that can underlie paradoxical embolism.[21,34,35]

When imaging techniques fail to detect a possible cardioembolic source, prolonged and repeated ambulatory monitoring of cardiac rhythm to detect paroxysmal atrial fibrillation is indicated, especially if palpitations occur or if left atrial enlargement is present. Chest x-ray films should be carefully evaluated for the presence of arteriovenous malformations. Even with vigorous efforts, some cardioembolic sources defy diagnosis. The small lesions of nonbacterial thrombotic (marantic) endocarditis usually are located on the atrial surface of the mitral valve and are notoriously difficult to detect echocardiographically. Early cardiomyopathies can present with embolism, despite normal electrocardiograms and echocardiograms.[15]

Should empiric treatment with anticoagulants be initiated for young people with ischemic stroke in whom embolism is suspected but in whom no cardioembolic source can be defined? When ischemia is recurrent and associated with features suggestive of embolism, anticoagulation should be considered, despite the uncertainties inherent in this situation. Frequent, thorough reevaluation should be undertaken in such patients, seeking definition of the stroke mechanism.

Stroke in young people is an uncommon problem. Establishing the cause of stroke is important, allowing specific therapy to minimize recurrent brain ischemia. Several newly recognized mechanisms of stroke that have been defined in young patients are known to affect all age groups. Cardioembolic sources are often occult, but have important treatment implications. When the cause of ischemic stroke in a young person is unclear after a thorough initial diagnostic evaluation, it is worthwhile to take a second look at the heart.

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